

REMARKS/ARGUMENTS

Throughout the amended claims the term “common dose bed” has been changed to a “target area of a dose bed”. This latter term is supported in the application as filed, e.g. paragraph [0026], [0028], [0081]-[0087].¹

Amended claim 21 corresponds to subject-matter of claim 21 filed on April 12, 2006 and subject-matter disclosed in the application as filed, especially in paragraphs [0009], [0018], [0019], [0025], [0075], [0081].

Amended claim 25 corresponds to subject-matter of claim 25 filed on April 12, 2006 and subject-matter disclosed in the application as filed, especially in paragraphs [0009], [0018], [0019], [0075].

Amended claim 26 corresponds to subject-matter of claim 26 filed on April 12, 2006 and subject-matter disclosed in the application as filed, especially in paragraphs [0009], [0018], [0019], [0075].

Amended claim 27 corresponds to subject-matter of claim 27 filed on April 12, 2006 and subject-matter disclosed in the application as filed, especially in paragraphs [0009], [0018], [0019], [0075]. In addition, the terms “interact” and “forming” has been replaced by “interacting” and “formation”, respectively, as kindly suggested by the Examiner.

Amended claim 28 corresponds to subject-matter of claim 28 filed on April 12, 2006.

Amended claim 30 corresponds to subject-matter of claim 30 filed on April 12, 2006 and subject-matter disclosed in the application as filed, especially in paragraphs [0009], [0018], [0019], [0075].

¹ Refer to paragraphs as numbered in the published version of the present application, U.S. 2004-0258625.

Amended claim 31 corresponds to subject-matter of claim 31 filed on April 12, 2006 and subject-matter disclosed in the application as filed, especially in paragraphs [0025], [0081].

Amended claim 33 corresponds to subject-matter of claim 33 filed on April 12, 2006 and subject-matter disclosed in the application as filed, especially in paragraphs [0009], [0018], [0019], [0075].

Amended claim 34 corresponds to subject-matter of claim 34 filed on April 12, 2006 and subject-matter disclosed in the application as filed, especially in paragraphs [0009], [0018], [0019], [0075].

Amended claim 35 corresponds to subject-matter of claim 35 filed on April 12, 2006 and subject-matter disclosed in the application as filed, especially in paragraphs [0009], [0018], [0019], [0075].

Amended claim 36 corresponds to subject-matter of claim 36 filed on April 12, 2006 and subject-matter disclosed in the application as filed, especially in paragraphs [0009], [0018], [0019], [0075]. In addition, the terms “interact” and “forming” has been replaced by “interacting” and “formation”, respectively, as kindly suggested by the Examiner.

Amended claim 37 corresponds to subject-matter of claim 37 filed on April 12, 2006 and subject-matter disclosed in the application as filed, especially in paragraphs [0009], [0018], [0019], [0075].

New claim 39 corresponds to subject-mater of claim 21 filed on April 12, 2006 and subject-matter disclosed in the application as filed, especially in paragraphs [0083], [0086], [0087].

New claim 40 corresponds to subject-mater of claim 31 filed on April 12, 2006 and subject-matter disclosed in the application as filed, especially in paragraphs [0083], [0086], [0087].

New Claims 41 and 42 are supported by paragraphs [0030] – [0035].

No new matter has been entered.

In the Office communication the following prior art documents were cited:

Haikarainen et al.	WO 00/64519 A1
Davies et al.	US 2002/0053344 A1
Clarke et al.	US 2002/0103260 A1

Haikarainen discloses a multi-dose dry powder inhaler (DPI), wherein the inhaler comprises two medicament containers, each containing a supply of medicament powder corresponding to a multitude of metered doses (page 3, lines 21–23). In connection with an inhalation, medicament powder from the two containers is transferred to a metering member equipped with two dosing recesses for receiving a metered dose of the respective powdered medicament (page 3, lines 23-25). The inhaler then has two aerosolization channels, each positioned over one of the two recesses (page 2, lines 29-31, page 4, lines 29-31). The metered doses are discharged simultaneously through the different aerosolization channels and are mixed first in the mouth piece or, if employing separate aerosolization channels, in the user's air channel or respiratory tract (page 2, lines 27-29; page 4, lines 34-37).

Haikarainen also teaches a method for inhalation using the described multi-dose dry powder inhaler. The method involves metering a dose of a first and a second powder medicament simultaneously from the respective supplies in the dry powder inhaler (page 3, lines 30-34). Thereafter the metered dose of the first medicament and the metered dose of the second medicament are brought simultaneously into the air flow path of the inhaler through separate flow paths (page 3, lines 34-37). The two doses are then inhaled through the inhaler and become mixed first at the air channel/respiratory tract of the inhaling patient (page 2, lines 28-29; page 3, lines 37-39).

In Haikarainen the separately metered powder quantities may therefore, in one particular embodiment, impinge separately onto the mouth piece of the inhaler device. In the issued Office action, the Examiner states at page 9 that the air channel in this mouth piece qualifies as a dose bed as used in the claims 21 and 31. Applicant respectfully disagrees that the person skilled in the art would take this view. In the present technical field, the term “dose bed” denotes an area onto which medical powder is deposited during a dose forming process. As a consequence, an air channel, or even a surface with which metered powder may temporarily collide as the powder is transported by an inhalation air stream during inhalation, hardly qualifies as a dose bed as used in the art.

In addition, the claims 21 and 31 specify that the pre-metered formulates are separately *deposited* onto a target area of the dose bed. The definition of this term “deposit” in Merriam-Webster’s Collegiate® Dictionary is “to place for safekeeping”. Thus, deposit powder on a dose bed implies placing the powder on the dose bed, where the powder is kept until use in form of inhalation. Any extremely short collision between powder and a mouth piece during inhalation does not qualify as deposition as defined within the art. However, as is evident from the discussion below, the claims 21 and 31 are still novel and inventive over Haikarainen irrespective of whether Haikarainen actually discloses separate depositing of pre-metered powder onto a dose bed.

Haikarainen never teaches another feature of the present invention, i.e. the sealing of the combined dose on the dose bed with a protective foil. In clear contrast, with the Examiner’s definition of the dose bed in Haikarainen, the powder will, even after colliding with the inner mouth piece surface, be transported by the inhalation air stream into the user’s mouth and respiratory tract. This further points to the fundamental differences between Haikarainen and the present invention. In Haikarainen, a dose comprising multiple medicaments is metered in connection with an inhalation occasion and this metering is

performed inside the DPI. The present invention teaches provision of medical products and pre-metered combined doses that are generated separate from the DPI and delivered as a physical entity that can be inserted into the DPI, where the sealed powder will be delivered.

Furthermore, Haikarainen never teaches that any sealed combined dose is designed for insertion into a DPI, where the combined dose becomes inhaled during the course of a single inhalation. In clear contrast, the combined dose of Haikarainen is produced inside the multi-dose DPI. This should be compared to the present invention as defined by claims 21 and 31, where the combined dose is generated and sealed outside of and separate from the DPI and will then be inserted into the DPI in connection with an inhalation.

As a consequence, the present invention as defined by the new claims is clearly novel over Haikarainen. In addition, the teachings of Haikarainen cannot be modified in any way to render the present invention obvious. For example, no sealing of the powder colliding with the mouth piece in Haikarainen is possible using a protective foil since the powder is actually carried by the inhalation air stream, and if any sealing would be possible no powder would of course be delivered to the user. There are further no evident modifications of Haikarainen's DPI that would result in a sealed combined dose that can be inserted into the DPI.

Haikarainen is also marred by several disadvantages in the form of gradient formation in the powder store of the inhaler and moisture leakage into the store. Powder technology is well aware of that powder containing a range of particle sizes, whether it is a perfect, ordered mixture or a single dry powder formulation, runs a risk of having small particles segregate from larger ones when the powder is being transported or handled in a metering process. For instance, small particles tend to fall to the bottom of a store by gravitation, so that over time the concentration of small active particles increases near the bottom of the store leading to depletion at the top of the store. A consequence of this is that

the fine particle dose of active agent in the metered doses will drift from too much to too little, or vice versa depending on the metering process, during the run of a metering process, although the metered dose mass is reasonably constant over the inhaler use time. As a result, the inhaled active dosage will vary considerably depending on whether the dose was produced early or late in a use time of the inhaler. This is not acceptable, of course.

Furthermore, by having a store of powder in the multi-dose DPI of Haikarainen, moisture will migrate into the powder and thereby cause the powder particles to agglomerate and aggregate into larger clusters, which in turn affects the gradient and size distribution discussed above, and makes it very hard to deliver fine particles at the desired location in the user's respiratory system. See for example, Keller et al. (U.S. Patent Application No. 10/628,965 and published under number 2004/0202616 A19) where Keller discusses the moisture problems that are inherent in multi-dose DPI (paragraph [0007], [0016]).

In Haikarainen, each dose is metered and generated inside the DPI. This means that the dose metering can take place in a high temperature and high moisture environment, depending on the current ambient conditions. The DPI of Haikarainen is also dependent on a movable recess that transports powder from a store chamber to an inhalation situation. As the person skilled in the art is well aware of, it is next to impossible to have completely moisture-tight DPIs with such movable parts. This should be compared to the present invention, where the powders are separately metered and deposited onto a dose bed and sealed in a controlled environment and not the user environment as Haikarainen.

Davies discloses an inhalation device that uses a medicament pack that comprises two sheets peelably secured to one another (paragraph [0004], [0041]). These two sheets define a plurality of medicament containers spaced along the length of the sheets (paragraph [0005]). In connection with inhalation, the two sheets are peeled apart a sufficient portion to

expose the contents of a dose pocket, which is being brought into alignment with a slot that is in connection with a nozzle (paragraph [0050]).

Davies teaches that medicaments can be delivered in combinations [0094]. In this context, Davies goes on saying that the formulations contain combinations of active ingredients. This means that at least two active ingredients are *mixed* together and provided in a single dose pocket.

Therefore Davies does **not** disclose a *separate* depositing of pre-metered powder quantities onto at least one target area of a dose bed.

The present invention as defined by the claims 21 and 31 is therefore clearly novel over Davies. Davies actually does not describe anything new that was not already discussed in the background section of the present invention. This means that the medicament pack of Davies is marred by problems and drawbacks in terms of mixing difficulties, problems in controlling the respective proportions of the active agents in the mixture, etc. mentioned in this background section.

Even if one were motivated to use a medicament pack, where the different dose pockets comprise different active agents, in such a case the combined dose is **not** adapted for delivery from a DPI during the course of a **single** inhalation. In clear contrast, a user must first inhale the first active agent contained in one dose pocket, then move the medicament pack up to the next subsequent dose pocket and then inhale the content of this next pocket in a new inhalation procedure. In addition to being cumbersome, such a solution furthermore has drawbacks in terms of difficulties for the user to know what active agents are contained in the different dose pockets.

The present invention, on the other hand, teaches that the e.g., formoterol and fluticasone medicament powders to be combined in a dose are metered and deposited *separately* onto at least one target area of a dose bed. The combined dose is then sealed by a

protective foil and constructed for insertion into a DPI where the combined dose becomes delivered during the course of a single inhalation.

Since Davies does not disclose or even suggest anything falling within the scope of the new claims and no obvious modification of Davies suggests the claims, the present invention as defined by the claims is considered patentable over Davies.

Clarke discloses inhalable compositions containing formoterol and fluticasone. Clarke discloses compositions in solution and dispersion forms as well as dry powder form. The positive therapeutic effects of combining the substances are well known in prior art. However, different methods and devices of supplying formoterol and fluticasone to a subject in need thereof are still being developed. Clarke's disclosure should be seen in this light.

Clarke teaches that a dry powder composition comprising a unit dose of selected amounts of formoterol and fluticasone in a *mixture* together with a suitable carrier (excipient) may be loaded into a capsule or blister (paragraph [0012]). The capsule or blister may then be made available in a dry powder inhaler and the powder mixture administered to a user.

Therefore Clarke does **not** teach that pre-metered quantities of the two active agents are deposited *separately* onto the at least one target area of the dose bed. In clear contrast, Clarke specifies that the two agents are provided as a mixture and not as separate constituents.

The Examiner specifies in the Office action that the suggested high quantity of excipient versus the two active agents (98.952 % w/w excipient, 0.048 % w/w formoterol fumarate dehydrate and 1.000 % w/w fluticasone propionate) will cause the two agents to be inherently separated by the lactose. This is not the case. In order to form an ordered powder mixture of active agent(s) and excipient, the content of the active agent(s) is limited to at most 4-5 % w/w of the mixture since higher content gives segregation problems. This means that the low active agent contents disclosed by Clarke will cause the small formoterol and

fluticasone particles to adhere to and be positioned onto the surface of the larger lactose particles. On these lactose particle surfaces, the two active agents will indeed interact. Furthermore, since an ordered mixture is disclosed by Clarke, the two active agents will be deposited together with the excipient onto a dose bed. Therefore it is not possible to obtain a *separate* deposition of powder quantities according to the teachings of Clarke. Therefore, the solution presented by Clarke amounts to nothing more than what was already discussed in the background section of the present application and is therefore marred by the problems identified in this section. In conclusion, the new claims are considered novel and patentable over Clarke.

Accordingly, and because none of the reference either alone or in combination disclose or suggest the subject matter of the newly presented claims, Applicants respectfully request the reconsideration and withdrawal of the outstanding rejections.

Finally, several provisional double patenting rejections have been presented. However, the claims have been changed herein, and in addition this case appears to be the first in line for Issuance. Accordingly, it is requested that this case be allowed to issue first, and that as the cases noted in the double patenting rejections proceed through examination and issue that the possibility of double patenting then be considered there against the fixed, issued claims deriving from this application.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Richard L. Treanor
Attorney of Record
Registration No. 36,379

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413 -2220
(OSMMN 06/04)